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Original Article

Impaired sleep and allostatic load: cross-sectional results from the Danish Copenhagen Aging and Midlife Biobank

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ABSTRACT

Objective: Understanding the mechanisms linking sleep impairment to morbidity and mortality is important for future prevention, but these mechanisms are far from elucidated. We aimed to determine the relation between impaired sleep, both in terms of duration and disturbed sleep, and allostatic load (AL), which is a measure of systemic wear and tear of multiple body systems, as well as with individual risk markers within the cardiac, metabolic, anthropometric, and immune system.
Methods: A cross-sectional population-based study of 5226 men and women from the Danish Copenhagen Aging and Midlife Biobank with comprehensive information on sleep duration, disturbed sleep, objective measures of an extensive range of biological risk markers, and physical conditions.
Results: Long sleep (mean difference 0.23; 95% confidence interval, 0.13, 0.32) and disturbed sleep (0.14; 0.06, 0.22) were associated with higher AL as well as with high-risk levels of risk markers from the anthropometric, metabolic, and immune system. Sub-analyses suggested that the association between disturbed sleep and AL might be explained by underlying disorders. Whereas there was no association between short sleep and AL, the combination of short and disturbed sleep was associated with higher AL (0.19; 0.08, 0.30) and high-risk levels of immune system markers.
Conclusion: Our study suggests small but significant differences in the distribution of allostatic load, a pre-clinical indicator of disease risk and premature death, for people with impaired relative to normal sleep. Impaired sleep may be a risk factor for developing disease and be a risk marker for underlying illness or sleep disorders.

1. Introduction

Whereas many studies have assessed the relationship between sleep and long-term morbidity [1,2], less attention has been directed at the more proximal mechanistic outcomes, which are imperative in drawing causal inference.

It has been proposed that long-term sleep impairment interferes with nightly physiological restitution and recovery of multiple body systems, with effects, for example, on neurendocrine and hormonal processes resembling those of chronic stress exposures [3]. In this regard, the concept of allostatic load (AL) may be interesting, as it refers to the physiological "wear and tear" resulting from chronic stress and inadequate recovery [4] and has been previously shown to be associated with risk of physical and mental disorders, e.g. depressive symptoms, burnout, cardiovascular disease, and premature death [5] – health outcomes previously linked to impaired sleep. As such, AL may constitute an important link between impaired sleep and later morbidity and mortality. AL is calculated using several biomarkers of endocrine, metabolic, cardiovascular, and immune functioning, and simultaneously captures changes across multiple biological systems [3,5]. This makes it possible to detect health risks at an early stage, when changes in individual parameters are still small.

Previous studies point to an intertwined nature between perceived stress, depression, and impaired sleep, with bidirectional mutually reinforcing relations [6], which complicates separation of the individual effects of these factors. Whereas previous studies have primarily focused on the association between psychological stress and AL [5], less attention has been directed at the potential for impaired sleep to act as an independent stressor affecting AL, as

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previously proposed by McEwen and van Cauter [3,7,8]. Further, studies on sleep and physiological mechanisms have primarily been experimental in design; addressing the effect of short-term controlled sleep restriction in rodents or a small number of predominantly young, healthy volunteers [7,9]. These studies found brief periods of sleep deprivation to affect individual components of AL, e.g. increase heart rate, blood pressure, and pro-inflammatory cytokine levels; alter cholesterol levels; and decrease insulin sensitivity and parasympathetic tone [8,10–17]. Results obtained from experimental studies cannot, however, be directly extrapolated to a general population of habitually short-duration sleepers. Further, several population-based studies have addressed the association between sleep and individual AL risk markers. Due to the interactive nature of risk markers, the association of sleep impairment with a cumulative measure such as AL might be more appropriate, but studies investigating this association are lacking.

Finally, research on sleep impairment and physiological functioning has mostly focused on the effects of sleep duration, and less on disturbed sleep, which may be another important aspect of impaired sleep adversely affecting nightly restitution [18]. Interactions between sleep duration and disturbed sleep have been supported with stronger effects of short sleep on cardiovascular and metabolic functioning in individuals simultaneously exposed to disturbed sleep [18–21].

Our hypothesis is that impaired sleep, both in terms of duration and disturbed sleep, has the ability to exert adverse effects on essential body systems, including the cardiac, metabolic, and immune systems, and anthropometric markers leading to higher levels of AL [3]. The objective of this study is to determine, for the first time, the relationship between impaired sleep (short, long, and/or disturbed sleep) and a cumulative measure of AL in a comprehensive population sample of 5226 men and women from the Danish Copenhagen Aging and Midlife Biobank (CAMB). Additionally, we determine the associations between impaired sleep and the component risk markers.

2. Methods

2.1. Study participants

Data for the current study are derived from CAMB, a Danish population-based study, combining detailed life-course information with measures of physiological functioning and health. Established in 2009–2011, CAMB is based on the population of three existing Danish cohorts: the Metropolit 1953 male birth cohort, the Danish Longitudinal Study of Work, Unemployment and Health, and the Copenhagen Perinatal Cohort. Cohort details have been published previously [22–24]. Of the 17,937 invited participants, 7191 agreed to participate (40% response) by completing a postal questionnaire. The questionnaire included detailed questions on health behavior, psychosocial factors, and physical conditions, enabling thorough adjustment for potential confounders. Participants underwent an extensive health examination including physiological tests and collection of blood samples for biological testing. The study protocol was approved by the local ethics committee (No. H-A-2008-126) and the Danish Data Protection Agency (No. 2008-41-2938). All participants gave informed consent at enrollment. Details of CAMB are described elsewhere [25]. This study included 5522 men and women who answered the questionnaire and delivered blood samples. Participants with incomplete biological information, missing information on sleep, or any of the covariates (n = 296) were excluded, leaving 1629 women and 3597 men for analyses.

2.2. Sleep impairment

Information on sleep duration was obtained by self-report as the average hours and minutes of weekday sleep, which we categorized into ≤6 h (short sleep), 7–8 h (reference category), and ≥9 h of sleep (long sleep). Disturbed sleep was assessed by the Karolinska Sleep Questionnaire (KSQ), which covers the frequency of symptoms of disturbed sleep: difficulties falling asleep, repeated awakenings, disturbed/uneasy sleep, and premature awakenings [26] with Cronbach's α of 0.83 in the CAMB sample. The five response categories ranged from (1) "every night/almost every night" to (5) "never". We created a binary measure to reflect a clinically significant level of disturbed sleep [27,28], with participants being considered to have disturbed sleep if they reported an average frequency of the included symptoms of "at least some times a week" (average response category ≤2). In order to address the combined effect of sleep duration and disturbed sleep, a variable reflecting the joint exposure with 7–8 h of undisturbed sleep as the joint reference was created.

2.3. Allostatic load risk markers

The biological measures considered in this study aimed at capturing cardiac, metabolic, and immune functioning, and included systolic and diastolic blood pressure (SBP, DBP), glycated hemoglobin (HbA_{1c}), triglycerides, the ratio of total cholesterol to high-density lipoprotein cholesterol (HDL/TC), high-sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6), and the anthropometric risk marker waist:hip ratio.

Collection and handling of biomarkers was undertaken in accordance with clinical guidelines described in Appendix S1.

A cumulative index of AL was composed to capture physiological dysregulation as the sum of risk markers (range, 0–7) with values exceeding clinically relevant cut-offs: SBP 140 mmHg and DBP 90 mmHg [29], hs-CRP 3 mg/dL [30], triglycerides 2.26 mg/dL [31], HbA_{1c} 6.5% [32], waist:hip ratio 1 for men [33], and 0.85 for women [34]; and HDL/TC <20% [31]. Because no clinical cut-off for IL-6 has been established, we used the 75th percentile corresponding to 2.90 mmol/L.

The most frequent approach to determine cut-offs for the individual risk markers, apart from the aforementioned method, is the application of distribution driven cut-offs based on the 75th percentiles. Although this ensures a certain degree of power, it comes at a price of comparability across studies, and the clinical relevance for exceeding an arbitrary threshold could be questioned. Further, as argued by Juster et al., the application of more general clinical cut-offs enables implementation of the results in clinical practice [35,36]. However, the distribution-driven approach was adopted in a sub-analysis of our study to assess the robustness of the results to the chosen AL measure.

2.4. Covariates

Covariates included age (continuous), sex and menopause (men, premenopausal women, postmenopausal women), time of blood sampling (continuous), cohabitation, educational attainment (no vocational training or semi-skilled worker, skilled worker, up to four years of theoretical training, more than four years of theoretical training, other), smoking status (never-smoker, ex-smoker, smoker of 1–14 g/day, smoker of 15–24 g/day, smoker of >24 g/day), alcohol consumption (0, 1–7, 8–14, 15–21, ≥22 units/week), and leisure time physical activity (<30 min/day, 30–60 min/day, >1 h/day). Perceived stress (continuous) was measured by the four-item version of the Perceived Stress Scale, a subscale of the Copenhagen Psychosocial Questionnaire [37] and depression (no/yes) by the Major Depression Inventory (DSM-IV) [38]. Both scales have previously shown acceptable psychometric properties in Danish population samples [37–39]. Cronbach's α was 0.81 and 0.90 for perceived stress and depression respectively in this CAMB sample. We used prior

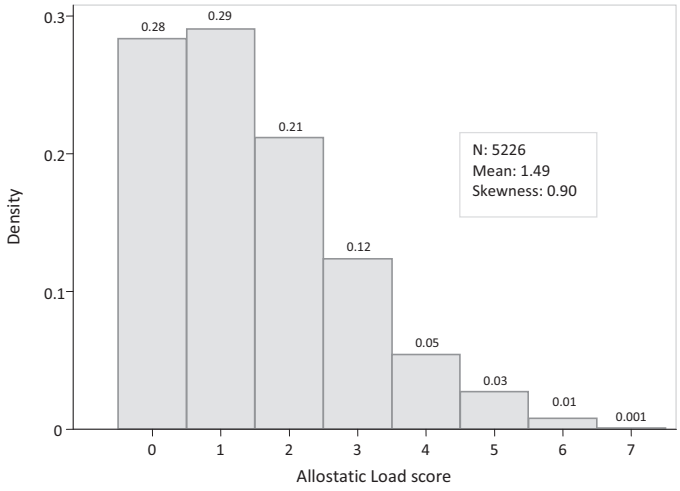

Fig. 1. Distribution of allostatic load among 5226 men and women participating in the Copenhagen Aging and Midlife Biobank Study, Denmark.

knowledge and the methods of directed acyclic graphs [40] to identify potential confounders.

2.5. Statistical methods

The distribution of AL was highly skewed with the majority of participants having none or just a single risk marker above the high-risk cut-offs (Fig. 1). Therefore, generalized linear models with a Poisson, rather than a Gaussian, distribution were fitted to determine the association between measures of impaired sleep and the level of AL. In the generalized linear model, an identity link function was used; subsequent effect measures will therefore reflect average differences between groups. Due to similarity of associations in the initial sex-specific analyses, the analyses were combined for women and men. First, age-, sex-, and time-of-sampling-adjusted differences in AL and 95% confidence intervals (CI) were estimated. Second, models were fitted to further adjust for potential confounding from cohabitation, educational attainment, and menopause. Third, due to the intertwined nature of impaired sleep with perceived stress and depression – constituting bidirectional mutually reinforcing relations [6] that made it hard to disentangle the temporality between these highly correlated factors – perceived stress and depression were added to the models in a separate step. Finally, since behavioral factors may be on either confounding or mediating pathways, smoking, alcohol consumption, and leisure time physical activity were added to the models in a final step of the analyses.

In a similar statistical framework, individual multiple logistic regressions were used to determine the association between the measures of impaired sleep and high-risk levels of the individual risk markers, in order to examine the contribution of individual markers to the overall index of AL.

In sensitivity analyses, the analyses of AL were restricted to normal-weight participants (BMI <25 kg/m^2) to investigate potential confounding from obstructive sleep apnea syndrome (OSA) (and other obesity-related sleep disorders) as the prevalence of OSA is much lower in this weight group. Analyses restricted to fasting participants were carried out to assess the potential effect of participants not being asked to fast before blood sampling. Since menopause is an important potential effect-modifier in analyses of biological components, additional analyses were performed according to menopausal status in women. In order to minimize the risk of reverse causation we undertook analyses restricted to participants without chronic respiratory disorders (asthma and chronic obstructive pulmonary disease), cardiovascular disease (acute myocardial infarction, angina pectoris, and stroke), cancers, or autoimmune disorders (chronic intestinal inflammation, arthritis, or connective tissue diseases). Analyses of AL substituting high waist:hip ratio with obesity (BMI ≥30 kg/m^2) was carried out to assess the impact of the chosen anthropometric measure. Finally, along the lines of previous research on AL, a sub-analysis with cut-offs based on the 75th percentiles (SBP ≥141 mmHg and DBP ≥92 mmHg, waist:hip ratio ≥0.98 for men and ≥0.90 for women, HbA_{1c} ≥5.62%, HDL/TC ≤0.19 [25th percentile], triglycerides ≥2.16 mg/dL, hs-CRP ≥2.4 mg/dL, IL-6 ≥2.90 mmol/L) was undertaken for the combined measure of AL.

3. Results

3.1. Characteristics of the CAMB study population

More than 25% of the participants reported sleeping <7 h per day, 5% slept on average ≥9 h, and 8% suffered frequently from disturbed sleep. Mean age was 54 years (range, 49–63). Whereas short sleepers did not differ substantially from those sleeping 7–8 h, more participants with long or disturbed sleep reported adverse health-related behaviors, existing chronic disorders, perceived stress, and depression (Table 1). The proportion of those living alone and having a low educational level was also higher among long and disturbed sleepers. The majority of the participants had none or one high-risk marker and <10% had more than three (Fig. 1). The average AL score was 1.5, which means that each participant on average had 1.5 risk markers above the high-risk cut-off.

3.2. Impaired sleep and allostatic load

Sleeping ≥9 h was associated with a higher level of AL compared to sleeping 7–8 h (mean difference, 0.23; 95% CI, 0.13, 0.32), whereas short sleep was not associated with the level of AL (Table 2). Participants reporting disturbed sleep had a higher mean AL than participants without this complaint (mean difference, 0.14: 0.06, 0.22). Assessment of the joint exposure of sleep duration and disturbed sleep (including the product term) showed no interaction between the two (P = 0.18). However, those with both short and disturbed sleep showed a higher mean AL (mean difference, 0.19: 0.08, 0.30) than those with 7–8 h of undisturbed sleep (Fig. 2). Even though perceived stress and depression were both associated with higher levels of AL in the current data (marginal mean difference, 0.09: 0.02, 0.17 and 0.24: 0.13, 0.35, respectively), additional adjustment for these did not explain the associations (Table 2).

Restricting the analyses to normal-weight participants (BMI <25 kg/m^2) showed results similar to the main analyses regarding the associations with sleep duration, whereas the association

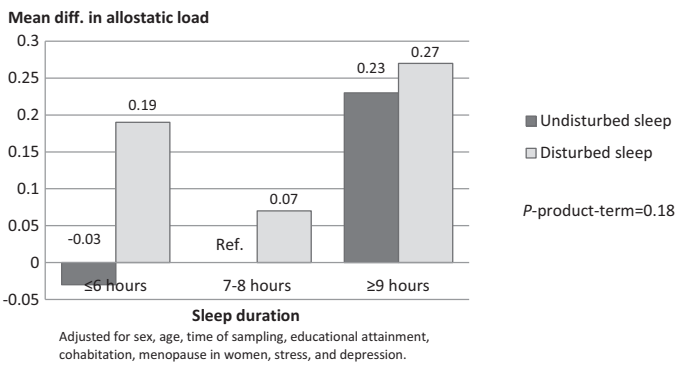

Fig. 2. Joint effects of sleep duration and disturbed sleep among 5226 men and women participating in the Copenhagen Aging and Midlife Biobank Study, Denmark.

Table 1
Characteristics of the 5226 men and women participating in the Copenhagen Aging and Midlife Biobank Study, Denmark.

Characteristics	Total population	Sleep duration			Disturbed sleep	
	(n = 5226)	≤6 h (n = 1367)	7–8 h (n = 3622)	≥9 h (n = 237)	No (n = 4828)	Yes n = 398)
Women, no. (%)	1629 (31)	348 (25)	1193 (33)	88 (37)	1460 (30)	169 (42)
Mean age (SD)	54 (4)	54 (4)	54 (4)	55 (4)	54 (4)	54 (4)
Low education, no. (%)[a]	346 (7)	101 (7)	211 (6)	34 (14)	299 (6)	47 (12)
Living alone, no. (%)	1023 (20)	294 (22)	660 (18)	69 (29)	898 (19)	125 (31)
Post-menopausal, no. (%)	904 (55)	201 (58)	651 (55)	52 (59)	790 (54)	114 (67)
Physically inactive, no. (%)[b]	1570 (30)	390 (29)	1062 (29)	118 (50)	1422 (29)	148 (37)
Smokers, no. (%)	1201 (23)	340 (25)	785 (22)	76 (32)	1072 (22)	129 (32)
High risk alcohol intake, no. (%)[c]	931 (18)	231 (17)	638 (18)	62 (26)	842 (17)	89 (22)
Obese, no. (%)[d]	762 (15)	206 (15)	501 (14)	55 (23)	675 (14)	87 (22)
PSS score >7, no. (%)[e]	477 (9)	162 (12)	276 (8)	39 (16)	346 (7)	131 (33)
Major depression (DSM-IV), no. (%)	165 (3)	52 (4)	79 (2)	34 (14)	95 (2)	70 (18)
Cardiovascular disorders, no. (%)[f]	339 (6)	93 (7)	204 (6)	42 (18)	285 (6)	54 (14)
Chronic respiratory disorders, no. (%)[g]	721 (14)	206 (15)	459 (13)	56 (24)	626 (13)	95 (24)
Cancers, no. (%)	41 (1)	14 (1)	22 (1)	5 (2)	32 (1)	9 (2)
Chronic inflammatory disorders, no. (%)[h]	1130 (22)	284 (21)	775 (21)	71 (30)	998 (21)	132 (33)

Abbreviations: BMI, body mass index; PSS, Percieved Stress Score; SD, standard deviation.
[a] No more than primary education.
[b] Physically active <30 min/day.
[c] More than 14 drinks/week for women and >21 drinks/week for men.
[d] BMI ≥30 kg/m^2.
[e] Ninetieth percentile of PSS (range, 0–16).
[f] Acute myocardial infarction, angina pectoris, and stroke.
[g] Asthma and chronic obstructive pulmonary disease.
[h] Chronic intestinal inflammation, arthritis or connective tissue diseases.

between disturbed sleep and AL was not apparent in this subsample (Table 3). In analyses restricted to fasting participants or to participants without known chronic physical disorders, AL remained associated with long, but not disturbed, sleep (Table 3). Subanalyses defining high-risk cut-offs according to the 75th percentiles (25th for HDL/TC) or substituting high waist:hip ratio with obesity in the AL measure did not change the conclusions of the main analyses (Table 3). Assessing the potential effect-modification by menopausal status suggested that the observed main effects of sleep on AL were stronger in men and in premenopausal women (data not shown).

3.3. *Impaired sleep and adverse levels of cardiac, metabolic, immune system, and anthropometric risk markers*

The proportion of participants with risk markers exceeding the high-risk cut-offs ranged from 2% for HbA_{1c} to 30% for waist:hip ratio. Among the assessed risk markers, short sleep duration was only associated with IL-6 (Table 4); those with both short and disturbed sleep had higher risk of adverse levels of immune system markers, triglycerides, and waist:hip ratio. Long sleepers suffered almost twice the odds of having a high waist:hip ratio [odds ratio (OR), 1.92; 95% CI, 1.44, 2.56] and were more than twice as likely to exceed the high-risk cut-off for HbA_{1c} (OR, 2.73; 1.51, 4.92) relative to those who slept 7–8 h. Long sleep was also associated with high-risk levels of hs-CRP (1.77; 1.32, 2.37) and IL-6 (1.39; 1.04, 1.86). Like long sleep, disturbed sleep was associated with several of the assessed risk markers across different body systems, including waist:hip ratio, HbA_{1c}, triglycerides, hs-CRP, and IL-6 in the multiple-adjusted analyses. These associations were slightly attenuated after further adjustment for perceived stress and depression.

4. Discussion

In this large population-based study, we found long sleep duration and disturbed sleep to be associated with higher AL and high-risk levels of anthropometric, metabolic, and immune system risk markers. Whereas no previous studies have assessed the association between impaired sleep and AL, our results are in line with previous studies supporting an association between AL and other stressors, e.g. psychological stress and depression [4,5]. Impaired sleep can be both a cause and a consequence of stress and depression, but additional adjustment for perceived stress and depression did not explain the associations observed in the current

Table 2
Impaired sleep and mean differences in allostatic load among the 5226 men and women participating in the Copenhagen Aging and Midlife Biobank Study, Denmark.

	N	Mean allostatic load (SD)	Age-, sex-, and time-adjusted differences in allostatic load (95% CI)	Multiple-adjusted[a] differences in allostatic load (95% CI)	+ Stress- and depression-adjusted differences in allostatic load (95% CI)	+ Lifestyle-adjusted[b] differences in allostatic load (95% CI)
Sleep duration						
≤6 h	1367	1.50 (1.40)	0.02 (–0.03 to 0.07)	0.01 (–0.04 to 0.06)	0.00 (–0.05 to 0.05)	0.00 (–0.05 to 0.05)
7–8 h	3622	1.46 (1.35)	Ref.	Ref.	Ref.	Ref.
≥9 h	237	1.99 (1.58)	0.31 (0.22 to 0.40)	0.25 (0.15 to 0.34)	0.23 (0.13 to 0.32)	0.14 (0.04 to 0.23)
Disturbed sleep						
No	4828	1.47 (1.36)	Ref.	Ref.	Ref.	Ref.
Yes	398	1.80 (1.53)	0.23 (0.15 to 0.31)	0.17 (0.09 to 0.25)	0.14 (0.06 to 0.22)	0.11 (0.02 to 0.19)

Abbreviations: CI, confidence interval; SD, standard deviation.
[a] Adjusted for sex, age, time of sampling, educational attainment, cohabitation, and menopause in women.
[b] Additionally adjusted for physical activity, smoking, and alcohol consumption.

Table 3
Impaired sleep and allostatic load: among sub-samples of the Copenhagen Aging and Midlife Biobank Study, Denmark, and with alternative compositions of allostatic load.

Impaired sleep and allostatic load	Sleep duration			Disturbed sleep	
	≤6 h	7–8 h	≥9 h	No	Yes
Exclusion of individuals with BMI ≥25 kg/m^2					
No.	594	1607	82	2119	164
Mean allostatic load (SD)	0.87 (1.04)	0.88 (1.00)	1.22 (1.14)	0.89 (1.02)	0.99 (1.04)
Multiple-adjusted[a] differences in allostatic load (95% CI)	–0.03 (–0.13 to 0.07)	Ref.	0.23 (0.02 to 0.43)	Ref.	0.08 (–0.08 to 0.24)
+ Stress- and depression-adjusted differences in allostatic load (95% CI)	–0.03 (–0.13 to 0.07)	Ref.	0.22 (0.02 to 0.43)	Ref.	0.09 (–0.08 to 0.26)
Exclusion of individuals with chronic diseases[b]					
No.	884	2410	111	3215	190
Mean allostatic load (SD)	1.39 (1.35)	1.36 (1.29)	1.75 (1.63)	1.37 (1.31)	1.53 (1.47)
Multiple-adjusted[a] differences in allostatic load (95% CI)	–0.004 (–0.07 to 0.06)	Ref.	0.21 (0.07 to 0.36)	Ref.	0.10 (–0.02 to 0.22)
+ Stress- and depression-adjusted differences in allostatic load (95% CI)	–0.004 (–0.07 to 0.06)	Ref.	0.20 (0.06 to 0.35)	Ref.	0.09 (–0.03 to 0.21)
Allostatic load defined by risk markers' 75th percentiles[c]					
No.	1367	3622	237	4828	398
Mean allostatic load (SD)	1.71 (1.57)	1.63 (1.54)	2.26 (1.74)	1.66 (1.55)	1.99 (1.75)
Multiple-adjusted[a] differences in allostatic load (95% CI)	0.01 (–0.04 to 0.06)	Ref.	0.27 (0.18 to 0.35)	Ref.	0.17 (0.10 to 0.25)
+ Stress- and depression-adjusted differences in allostatic load (95% CI)	0.003 (–0.05 to 0.05)	Ref.	0.24 (0.15 to 0.33)	Ref.	0.14 (0.06 to 0.22)
Exclusion of non-fasting participants					
No.	507	1355	91	1780	173
Mean allostatic load (SD)	1.54 (1.39)	1.59 (1.38)	2.12 (1.63)	1.58 (1.39)	1.77 (1.48)
Multiple-adjusted[a] differences in allostatic load (95% CI)	–0.04 (–0.12 to 0.04)	Ref.	0.23 (0.09 to 0.38)	Ref.	0.11 (–0.01 to 0.22)
+ Stress- and depression-adjusted differences in allostatic load (95% CI)	–0.05 (–0.13 to 0.04)	Ref.	0.22 (0.06 to 0.37)	Ref.	0.07 (–0.06 to 0.20)
Allostatic load substituting high-risk waist:hip ratio with obesity[d]					
No.	1367	3622	237	4828	398
Mean allostatic load (SD)	1.37 (1.38)	1.30 (1.34)	1.74 (1.59)	1.32 (1.35)	1.58 (1.55)
Multiple-adjusted[a] differences in allostatic load (95% CI)	0.01 (–0.04 to 0.06)	Ref.	0.24 (0.14 to 0.34)	Ref.	0.18 (0.10 to 0.27)
+ Stress and depression adjusted differences in allostatic load (95% CI)	0.005 (–0.05 to 0.06)	Ref.	0.22 (0.12 to 0.32)	Ref.	0.15 (0.06 to 0.24)

Abbreviations: BMI, body mass index; CI, confidence interval; SD, standard deviation.
[a] Adjusted for sex, age, time of sampling, educational attainment, cohabitation, and menopause in women.
[b] Cardiovascular (acute myocardial infarction, angina pectoris, and stroke), pulmonary (asthma, and chronic obstructive pulmonary disease), autoimmune disorders (chronic intestinal inflammation, arthritis or connective tissue diseases) or cancers.
[c] SBP ≥141 mmHg and DBP ≥92 mmHg, waist:hip ratio ≥0.98 for men ≥0.90 for women, HbA_{1c} ≥5.62% (25th percentile) HDL:TC ≤0.19, triglycerides ≥2.16 mg/dL, hs-CRP ≥2.4 mg/dL, IL-6 ≥2.90 mmol/L.
[d] BMI ≥30.

study. Our results are thus consistent with the idea that the association between impaired sleep and AL extend beyond what is explained by perceived stress and depression. As proposed by McEwen and others, AL may arise from insufficient recovery, and thus it is possible that impaired sleep increases AL by disrupting recovery processes [3,7,8]. However, sub-analyses indicated that especially disturbed sleep might be an indicator of underlying obesity-related disorders, e.g. sleep apnea or chronic physical disorders, in accordance with studies showing associations between AL and chronic disorders such as cardiovascular disease and diabetes [5]. Short sleep was not consistently found to be associated with AL in this population, although those who suffered both short and disturbed sleep showed higher AL levels and high-risk levels of immune markers, triglycerides, and waist:hip ratio. Despite this, we found limited indication of an interaction between sleep duration and disturbed sleep.

Although this is the first study to address the association between impaired sleep and the combined measure of AL, some previous studies have assessed the association between measures of impaired sleep and individual risk markers. Contrary to our findings, controlled experimental studies support a negative effect of sleep deprivation on measures of glucose metabolism and insulin sensitivity [8,41]. Previous population studies have primarily assessed the association between sleep and diabetes, and a recent meta-analysis found both quantity (short and long sleep) and quality of sleep to consistently predict the risk of type-2 diabetes [42]. A few studies comprising restricted population samples have yielded inconclusive results regarding the association between sleep duration, disturbed sleep and HbA_{1c}, but there is some indication of a U-shaped association with sleep duration [43,44] and associations with symptoms of disturbed sleep [45,46]. Our results are largely consistent with the studies supporting an effect of long sleep on HbA_{1c}, whereas we found no association with short sleep. In our study, limited power hampered the assessment of an association between disturbed sleep and HbA_{1c}.

Population-based studies on sleep and different measures of obesity have shown conflicting results, with some suggesting a U-shaped association between sleep duration and obesity, mainly in cross-sectional studies [8,41,47,48]. Our findings are partly in contrast to those studies, as we find no association between short sleep and waist:hip ratio. We do, however, find a higher risk of central obesity among those with long or disturbed sleep.

We found no evidence for an association between impaired sleep and hypertension in the present study, and results from previous studies have been mixed [19]. In the Coronary Artery Risk Development in Young Adult sleep study, actigraphy-measured sleep duration as well as sleep maintenance were associated with higher levels and adverse changes in blood pressure in a population sample of 578 men and women aged 33–45 years [49]. Meanwhile, only short sleep duration predicted the risk of hypertension in the CARDIA study. A recent review supported a higher prevalence of hypertension in people with long sleep based on cross-sectional data, and an effect of short sleep on onset of hypertension, which might be more pronounced (or even restricted to) in individuals aged <60 years [50] and/or women [19]. In contrast to our findings, associations between symptoms of disturbed sleep, such as difficulties initiating or maintaining sleep, and hypertension are generally supported in the literature, especially in combination with short sleep [19,51].

In one of the largest studies on sleep impairment and inflammatory markers to date, we found short, long, and disturbed sleep to be associated with high levels of inflammatory markers. An association between sleep restriction and inflammatory markers including hs-CRP and IL-6 is also supported by experimental data, but

Table 4
Impaired sleep and odds ratios for high levels of anthropometric, cardiovascular, metabolic, and immune system risk markers among 5226 men and women participating in the Copenhagen Aging and Midlife Biobank Study, Denmark.

Risk markers	Sleep duration			Disturbed sleep	
	≤6 h (n = 1367)	7–8 h (n = 3622)	≥9 h (n = 237)	No (n = 1460)	Yes (n = 169)
Cardiovascular risk markers					
Hypertension (≥140/90 mmHg)					
No. of cases	289	780	49	1035	83
Multiple-adjusted[a] OR (95% CI)	0.93 (0.80 to 1.09)	Ref.	0.92 (0.66 to 1.29)	Ref.	1.06 (0.81 to 1.37)
+ Stress- and depression-adjusted OR (95% CI)	0.93 (0.80 to 1.09)	Ref.	0.94 (0.67 to 1.31)	Ref.	1.11 (0.84 to 1.46)
Anthropometric risk markers					
Waist:hip (men ≥1.0, women ≥0.85)					
No. of cases	388	1074	115	1402	175
Multiple-adjusted[a] OR (95% CI)	1.05 (0.90 to 1.21)	Ref.	1.99 (1.49 to 2.65)	Ref.	1.53 (1.22 to 1.92)
+ Stress- and depression-adjusted OR (95% CI)	1.03 (0.89 to 1.19)	Ref.	1.92 (1.44 to 2.56)	Ref.	1.41 (1.11 to 1.79)
Metabolic risk markers					
HbA_{1c} (≥6.50%)					
No. of cases	35	71	16	106	16
Multiple-adjusted[a] OR (95% CI)	1.22 (0.80 to 1.84)	Ref.	3.15 (1.78 to 5.58)	Ref.	1.73 (1.00 to 3.00)
+ Stress- and depression-adjusted OR (95% CI)	1.17 (0.77 to 1.77)	Ref.	2.73 (1.51 to 4.92)	Ref.	1.29 (0.71 to 2.34)
HDL/total cholesterol (≤0.20)					
No. of cases	396	1034	74	1395	109
Multiple-adjusted[a] OR (95% CI)	0.92 (0.80 to 1.06)	Ref.	1.18 (0.88 to 1.59)	Ref.	1.02 (0.80 to 1.30)
+ stress- and depression-adjusted OR (95% CI)	0.92 (0.80 to 1.07)	Ref.	1.22 (0.90 to 1.65)	Ref.	1.07 (0.83 to 1.38)
Triglycerides (≥2.26 mg/dL)					
No. of cases	307	787	61	1058	97
Multiple-adjusted[a] OR (95% CI)	0.96 (0.82 to 1.12)	Ref.	1.22 (0.89 to 1.67)	Ref.	1.24 (0.97 to 1.59)
+ Stress- and depression-adjusted OR (95% CI)	0.94 (0.81 to 1.10)	Ref.	1.19 (0.87 to 1.63)	Ref.	1.14 (0.88 to 1.48)
Immune system risk markers					
hs-CRP (≥3 mg/dL)					
No. of cases	269	675	76	913	107
Multiple-adjusted[a] OR (95% CI)	1.04 (0.88 to 1.22)	Ref.	1.84 (1.38 to 2.46)	Ref.	1.42 (1.12 to 1.80)
+ Stress- and depression-adjusted OR (95% CI)	1.02 (0.87 to 1.20)	Ref.	1.77 (1.32 to 2.37)	Ref.	1.32 (1.02 to 1.69)
IL-6 (≥2.90 pg/mL)					
No. of cases	369	851	81	1172	129
Multiple-adjusted[a] OR (95% CI)	1.17 (1.02 to 1.36)	Ref.	1.50 (1.12 to 1.99)	Ref.	1.43 (1.14 to 1.80)
+ Stress- and depression-adjusted OR (95% CI)	1.16 (1.01 to 1.34)	Ref.	1.39 (1.04 to 1.86)	Ref.	1.31 (1.03 to 1.66)

Abbreviations: CI, confidence interval; HbA_{1c}, glycated hemoglobin; HDL, high-density lipoprotein cholesterol; hs-CRP, high sensitivity C-reactive protein; IL-6, interleukin-6; OR, odds ratio.

[a] Adjusted for sex, age, time of sampling, educational attainment, cohabitation, and menopause in women.

results from representative population samples are scarce and have shown mixed results [52]. There is, however, evidence to suggest associations between both sleep duration and sleep disturbances with inflammatory markers, including IL-6 and hs-CRP, with associations generally being stronger in women than in men [9].

In general, vast differences in study designs, study populations, applied risk markers and definition of high-risk levels, analytical approaches, and lack of consistent assessment of disturbed sleep in previous studies may explain some of the inconsistency in the results presented above. Large representative population-based studies, such as the present, are needed to further explore the association between impaired sleep, individual risk markers and AL.

4.1. Strengths and limitations

The strengths of the current study include the large population-based data material with standardized and validated collection of a large number of risk markers. Careful collection of risk markers from different body systems along with information on both sleep duration and disturbed sleep enabled, for the first time, comprehensive assessment of the association between impaired sleep and AL – a pre-clinical indicator of disease risk. Furthermore, detailed information on a range of demographic, socio-economic, behavioral, and psychological risk factors enabled thorough adjustment for potential confounding. Assessment of perceived stress and depression through validated measures enabled exploration of the intertwined relations between impaired sleep, perceived stress, and depression. However, with previous studies pointing to associations between AL and mental disorders – e.g. chronic stress, burnout, and depression, which are intricately linked to impaired sleep – future longitudinal studies should assess the complex interplay between impaired sleep, mental health, and AL with consideration of the temporal relations to further understand the underlying mechanisms linking impaired sleep to disease.

The cross-sectional nature of our study prevents us from directly distinguishing cause from effect, and the relationship between impaired sleep and disease is most likely bidirectional. Long sleep is likely to be a consequence of, or a marker for, ill health, and we also found that the association between disturbed sleep and AL was mainly confined to those with existing chronic disorders. However, the association between long sleep and AL remained in the healthy sub-sample, suggesting an association not explained by already established disease.

There is no consensus on how to best measure AL [5] and one could question whether a different operationalization of AL would have altered the results. Sensitivity analyses determining cut-offs based by the 75th percentiles, a frequently applied method, yielded similar results to the clinically determined cut-offs. Inclusion of exact risk markers varies by study and some studies also include endocrine measures, such as cortisol [5]. Although such measures unfortunately were not available to us, previous studies on sleep and cortisol have shown increased evening cortisol levels in association with laboratory sleep restriction [3,13], self-reported short sleep [53], and disturbed sleep [53,54]. The inability to include

cortisol along with other potentially important risk markers might have contributed to conservative estimates of the association between impaired sleep and AL in our study.

Blood samples were collected non-fasting, which could have affected the concentration of some but not all risk markers, although a recent large-scale study found only a weak association between fasting time and lipid levels among >200,000 individuals [55]. Nonetheless, since blood samples were attained between 07:00 and 17:00 and both time of sampling and time since last meal may depend on participants' sleeping habits, all analyses were adjusted for time of sampling, and this is not likely to be a major source of bias in our study. Further, participants reported whether they had consumed any food or beverages within 2 h of sampling. Analyses restricted to participants who reported to have fasted showed associations with sleep duration similar to the main analyses; allostatic load was independent of disturbed sleep in this sub-sample, thus highlighting the need for future studies to obtain fasting blood samples.

Only 40% of those invited to participate in CAMB completed the questionnaire and 31% attended the study clinic for physical testing and blood samples. Comparing national register data for participants and non-participants indicated that CAMB participants may be a somewhat selected group, with a smaller proportion being unemployed compared to non-participants [25]. However, there were no apparent health differences between participants and non-participants, with similar average number of contacts with the general practitioner, who serves as a gatekeeper for more specialized treatment in Denmark, and we doubt that selection mechanisms could explain our results.

Impaired sleep was assessed by self-report, which may have resulted in some misclassification. Whereas polysomnography would have more accurately reflected sleeping patterns including the presence of sleep disorders, it is unfeasible to perform in large population settings. Self-reported sleep therefore remains our primary source of information on sleep patterns in the general population. Some studies have found fairly strong correlations between direct assessments of sleep duration and more subjective measures [56,57], and studies of the KSQ have indicated close correspondence of the frequency of sleep disturbances with an electroencephalographically validated sleep diary [58].

We were unable to account for the potential effects of underlying clinical sleep disorders including sleep apnea, a potential cause of both impaired sleep and adverse levels of several risk markers [59]. In an attempt to minimize this effect, sensitivity analyses restricted to normal-weight participants, in which sleep apnea and other sleep disorders are relatively rare, were carried out. In this subsample, disturbed sleep was no longer associated with AL, suggesting that the experience of disturbed sleep may, in fact, be an indicator of obesity-related conditions, e.g. an underlying sleep disorder. Future studies should aim to include objective measures of sleep disorders such as sleep apnea, in order to address how these affect the relationship between impaired sleep and AL.

In summary, this study suggests small but significant differences in the distribution of AL for people with impaired relative to normal sleep. Specifically, we found long sleep duration and disturbed sleep to be associated with higher AL, a pre-clinical indicator of disease risk and premature death, and high-risk levels of anthropometric, metabolic, and immune risk markers. Short and disturbed sleep in combination was also associated with higher AL and several risk markers, whereas short sleep by itself was not found to be an individual risk factor for AL. Despite the small scale of these differences, poor sleep is a frequent problem affecting a vast number of people in modern society. Thus even smaller differences in the distribution of AL associated with impaired sleep can yield substantial impact at the population level.

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Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2014.07.013.

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Appendix: Supplementary material

Supplementary data to this article can be found online at doi:10.1016/j.sleep.2014.07.013.

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